The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2018; 25: 720-732. http://doi.org/10.5551/jat.43240

Clinical and Imaging Characteristics of Cerebral Infarction in Patients with Nonvalvular Atrial Fibrillation Combined with Cerebral Artery Stenosis

Wei Sun[1], Guangsheng Li[1], Xiangjun Zeng[1], Zhaohui Lai[1], Mingqi Wang[1], Yi Ouyang[1], Guoyong Zeng[1], Jidong Peng[2], Junyuan Zhong[2], Daoxiong Xiao[2], Zhiping Huang[3] and Xiaofen Guo[3]

[1]Department of Neurology, the Affiliated Ganzhou Hospital of Nanchang University, Jiangxi, China
[2]Department of Radiology, the Affiliated Ganzhou Hospital of Nanchang University, Jiangxi, China
[3]Department of Ultrasonography, the Affiliated Ganzhou Hospital of Nanchang University, Jiangxi, China

Aims: Nonvalvular atrial fibrillation often occurs in combination with carotid atherosclerosis, but less is known about it in combination with cerebral artery stenosis. This study investigated the characteristics of cerebral infarction in patients with nonvalvular atrial fibrillation with or without cerebral artery stenosis.

Methods: A retrospective analysis was conducted on 172 cerebral infarction patients with nonvalvular atrial fibrillation hospitalized at the Affiliated Ganzhou Hospital of Nanchang University between December 2011 and January 2016. The patients were divided into two groups (stenosis and non-stenosis groups) based on whether the cerebral infarction was combined with cerebral artery stenosis or not. Clinical characteristics, related supplementary examination, and the imaging characteristics of cerebral infarction lesions were compared between the groups.

Results: Mean age [(75.73 ± 8.46) years vs. (63.44 ± 9.95) years], National Institute of Health stroke scale (NIHSS) score [(8.66 ± 6.73) vs. (4.59 ± 3.51)], CHA_2DS_2-VASc score [(2.93 ± 1.40) vs. (0.96 ± 0.98)], history of hypertension (74.4% vs. 30.0%), and history of stroke/ transient ischemic attack (TIA) (55.8% vs. 13.3%) were higher in the stenosis group (n=107) than in the non-stenosis group (n=65) (P<0.01). In the stenosis group, there were different types of cerebral infarction lesions, including multiple infarction (multifocal type), massive infarction, watershed infarction, and lacunar infarction; in the non-stenosis group, the 60.0% lesions were multiple infarction (multifocal type), a significantly higher proportion than the stenosis group (26.2%, P<0.05). NIHSS score was an independent risk factor for worse prognosis at follow-up (OR (95%CI) 1.251–1.674, P<0.001).

Conclusions: Advanced age, hypertension, and stroke/TIA were increased in patients with cerebral infarction with nonvalvular atrial fibrillation combined with cerebral artery stenosis.

Key words: Nonvalvular atrial fibrillation, Cerebral infarction, Cerebral artery stenosis, Diffusion-weighted imaging

Introduction

Nonvalvular atrial fibrillation (NVAF) is the most common type of atrial fibrillation and an independent risk factor for cerebral infarction; about 20% of the cases of cerebral infarction are cardiogenic cerebral infarction and, of these, nearly 50% are caused by NVAF[1, 2]. Both mortality and recurrence rate of cerebral infarction patients with atrial fibrillation are higher than that of cerebral infarction patients without atrial fibrillation[3]. Understanding the risk factors for cerebral infarction in patients with NVAF relies on the reasonable assessment of the risk of complicated cerebral infarction. These risks can then guide strategies for the prevention of thromboembolism. Clinicians can use the CHA_2DS_2-VASc score as a way of

Address for correspondence: Guangsheng Li, Department of Neurology, the Affiliated Ganzhou Hospital of Nanchang University, Ganzhou 341000, Jiangxi, China E-mail: liguangsheng0016@163.com

Received: October 26, 2017 Accepted for publication: April 23, 2018

assessing the risk for embolism and stroke in patients with atrial fibrillation. This score assigns a level of risk based on the patient's history of congestive heart failure, arterial hypertension, age, diabetes mellitus, status post stroke or transient ischemic attack, vascular disease, and female sex[4]. Nevertheless, due to the controversies in the prediction efficiency of current risk stratification schemes for stroke and unclear mechanisms of cerebral infarction in patients with NVAF, there may be some more important risk factors for the occurrence of stroke in patients with atrial fibrillation[5, 6].

At present, the high-risk factors of cerebral infarction in patients with NVAF, such as age, hypertension, and diabetes, are all recognized as being risk factors of atherosclerosis[7]. Aortic arch atherosclerosis may be involved in the occurrence of stroke in atrial fibrillation[8, 9]. Studies have also demonstrated that about 70% of patients with NVAF have carotid atherosclerosis and approximately 20%–50% of patients with NVAF have severe carotid artery stenosis[10, 11], which can further increase the risk of cerebral infarction in patients with NVAF[12, 13]. During our clinical observations, we also found that some cerebral infarction patients with NVAF also had cerebral atherosclerosis. Therefore, we consider that cerebral artery stenosis may also play an important role in causing stroke in NVAF. As previous studies have mostly focused on peripheral or extracranial arteries, reports of cerebral infarction in patients with NVAF combined with cerebral artery stenosis are rare.

The aim of this study was to investigate the clinical and imaging characteristics of cerebral infarction in patients with NVAF with or without cerebral artery stenosis. The results should provide important information about cerebral infarction with NVAF in combination with cerebral artery stenosis.

Subjects and Methods

Study Design

This was a retrospective analysis of patients with NVAF hospitalized for cerebral infarction at the Department of Neurology of the Affiliated Ganzhou Hospital of Nanchang University between December 2011 and January 2016.

The study was approved by the ethics committee of the Affiliated Ganzhou Hospital of Nanchang University.

Patients

Patients were included in the study if they fulfilled the following inclusion criteria: 1) older than 18 years and 2) preliminarily diagnosed as having cerebral infarction with NVAF. Cerebral infarction was diagnosed according to the Framingham criteria[14] if it met the following criteria: 1) acute onset; 2) the emergence of focal neurological deficits (one side of the face or limb numbness, speech disorders, etc.), a small number of patients with comprehensive neurological deficits; 3) symptoms or signs continued for more than 30 min; and 4) brain magnetic resonance imaging (MRI) showed acute ischemic lesions. Atrial fibrillation was diagnosed according to the following criteria: 1) patients with a previous history of atrial fibrillation; or 2) duration of atrial fibrillation lasting over 30 s, showing an absence of P-wave replaced by F-wave of absolutely irregular amplitude, shape, and spacing (frequency, 350–600 times/min) in electrocardiogram.

The exclusion criteria were: 1) intracerebral hemorrhage; 2) atrial fibrillation associated with reversible causes (which included acute myocardial infarction, acute myocarditis, untreated hyperthyroidism, atrial fibrillation caused by electrophysiological examination, angiography and pacemaker operation, and recent history of cardiothoracic surgery); or 3) rheumatic heart valve disease confirmed by clinical diagnosis and ultrasonic echocardiography.

The patients were grouped into two groups according to the diagnostic criteria of cerebral artery stenosis. Patients with NVAF combined with cerebral artery stenosis were placed in the stenosis group, and those with NVAF without cerebral artery stenosis were placed in the non-stenosis group.

The diagnosis of cerebral artery stenosis referred to a stenosis degree of any segment of the cerebral artery ≥ 50%[15, 16] but excluded isolated symptomatic artery stenosis related to the cerebral infarction area. Multiple cerebral artery stenosis referred to lesions involving more than one segment of cerebral arteries. Cerebral artery stenosis included extracranial artery stenosis and intracranial artery stenosis. The extracranial arteries were divided into different segments: common carotid artery, external carotid artery, extracranial internal carotid artery (E-ICA), and extracranial vertebral artery (E-VB). The intracranial arteries were also divided into various segments: intracranial internal carotid artery (I-ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), intracranial vertebral artery (I-VA), basilar artery, and posterior cerebral artery (PCA).

Data Collection

Case data were retrospectively studied, including clinical characteristics and basic data (gender and age); past medical history and personal history (history of stroke/TIA, hypertension, diabetes, coronary heart disease, and smoking and alcohol consumption); pre-

vious history of medication (antiplatelet and anticoagulant drugs); condition assessment (NIHSS score) and risk assessment for recurrent stroke (CHA_2DS_2-VASc score[17]); data on supplementary examinations (serum biochemistry: total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and homocysteine (Hcy)); fibrinogen (Fib) and international normalized ratio (INR); and heart color Doppler examination (ejection fraction (EF) and left atrial diameter).

Craniocerebral magnetic resonance angiography (MRA), transcranial Doppler ultrasonography, and carotid color ultrasound were performed for all patients within 3 days after admission to hospital. The intracranial arteries were examined using craniocerebral MRA and transcranial Doppler ultrasound. The extracranial arteries were examined by carotid color ultrasound. The imaging of the cerebral infarction lesions in the present study was analyzed by two neurologists and two radiologists specialized in magnetic resonance diagnostic, each with >7 years of relevant experience. Acute cerebral infarction lesions were determined based on high signal intensity on diffusion-weighted imaging and low signal intensity on apparent diffusion coefficient. The types of cerebral infarction lesions were divided according to single lesion and multiple lesions (which referred to discontinuous lesions in each layer, whereas unseparated lesions were considered as single lesion). According to the anatomical sites of infarction lesions, a single lesion was further divided into cortical infarction, subcortical infarction (infarction lesion <15 mm in diameter was considered as lacunar infarction[18]), cortical-subcortical infarction, watershed infarction, and brain stem and cerebellar single infarction. Based on the size of the lesion area, cerebral infarction lesions were divided into massive cerebral infarction (the maximum diameter of lesion ≥ 40 mm)[19] and non-massive cerebral infarction (the maximum diameter of lesion <40 mm).

Follow-Up

Follow-up was performed 90 days after the patients were discharged, via telephone or face to face when some of the patients returned to the hospital for re-examination. Follow-up evaluation was undertaken by clinicians who had received unified training on the classification of the mRankin grade, and they had no previous interaction with the patients. The patients, relatives, or care workers who had taken care of the patients for a long time were questioned. Good prognosis was defined as mRankin score ≤ 2. Poor prognosis was defined as mRankin score ≥ 3.

Statistical Analysis

Statistical analysis was carried out using Windows SPSS (Version 18.0; IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared by the two independent-samples t-test. Categorical variables were compared using the chi-square test of fourfold table (when theoretical frequency was <5, Fisher's exact probability test for fourfold table data was applied). One-way analysis of variance with the post hoc LSD test for continuous variables and chi-square test for categorical variables were used for subgroup analyses. The baseline data of the good vs. poor prognosis group were first compared using univariate analyses. Then, multivariate logistic regression analysis was carried out on the factors with significant difference ($P<0.05$). $P<0.05$ was considered as statistically significant.

Results

From December 2011 to January 2016, 1563 patients with acute cerebral infarction who were hospitalized at the Department of Neurology of the Affiliated Ganzhou Hospital of Nanchang University were considered for inclusion in the study. Among them, 1313 patients without atrial fibrillation and 45 patients with combined rheumatic valvular heart disease were excluded. In addition, another 33 patients were excluded due to incomplete vascular examination. Finally, 172 cerebral infarction patients with NVAF were consecutively enrolled, with 93 males and 79 females (mean age, 70.85 ± 10.86 years). The stenosis group included 107 patients (62.2%); 64 males (59.8%) and 43 females (40.2%); average age, 75.73 ± 8.46 years. The non-stenosis group included 65 patients (37.8%); 31 males (47.7%) and 34 females (52.3%); mean age, 63.44 ± 9.95 years (**Table 1**).

Comparison of the Clinical Characteristics

Compared with the non-stenosis group, the stenosis group showed higher mean age [(75.73 ± 8.46) years vs. (63.44 ± 9.95) years; $P<0.001$], NIHSS score [(8.66 ± 6.73) vs. (4.59 ± 3.51); $P=0.003$], CHA_2DS_2-VASc score [(2.93 ± 1.40) vs. (0.96 ± 0.98); $P<0.001$], and the proportion of patients with a history of hypertension (74.4% vs. 30.0%; $P<0.001$) and history of stroke/TIA (55.8% vs. 13.3%; $P<0.001$). No statistical differences were detected in gender, history of diabetes, history of heart failure, history of smoking, history of alcohol consumption, history of antiplatelet drugs, or history of anticoagulant drugs between the two groups ($P>0.05$) (**Table 1**).

Table 1. Clinical characteristic of the stenosis and non-stenosis groups

Variables	Stenosis group (n = 107)	Non-stenosis group (n = 65)	P
Gender, n (%)			0.322
Male	64 (59.8)	31 (47.7)	
Female	43 (40.2)	34 (53.3)	
Age (years), mean ± SD	75.73 ± 8.46	63.44 ± 9.95	< 0.001
History of stroke/TIA, n (%)	59 (55.1)	9 (13.8)	< 0.001
Coronary artery disease, n (%)	20 (18.7)	6 (9.2)	0.093
Hypertension, n (%)	80 (74.7)	18 (27.7)	< 0.001
Diabetes, n (%)	16 (14.9)	7 (10.7)	0.434
Heart failure, n (%)	11 (10.2)	8 (12.3)	0.681
Peripheral vascular disease, n (%)	13 (12.1)	5 (7.7)	0.354
CHA_2DS_2-VASc score, mean ± SD	2.93 ± 1.40	0.96 ± 0.98	< 0.001
Smoking, n (%)	47 (43.9)	21 (32.3)	0.131
Alcohol consumption, n (%)	42 (39.2)	17 (26.2)	0.079
NIHSS score, mean ± SD	8.66 ± 6.73	4.59 ± 3.51	0.003
History of antiplatelet drugs, n (%)	38 (35.5)	15 (23.1)	0.067
History of anticoagulant drugs, n (%)	8 (7.4)	6 (9.2)	0.683
LDL-C (mmol/L), mean ± SD	2.53 ± 0.69	2.66 ± 0.66	0.449
TC (mmol/L), mean ± SD	3.96 ± 0.94	4.04 ± 1.25	0.778
TG (mmol/L), mean ± SD	1.49 ± 0.83	1.59 ± 0.94	0.637
INR, mean ± SD	1.13 ± 0.18	1.17 ± 0.41	0.586
Fib (g/L), mean ± SD	3.19 ± 0.86	2.91 ± 0.92	0.198
Hcy (μmol/L), mean ± SD	13.30 ± 8.97	15.37 ± 12.17	0.421
EF (%), mean ± SD	66.79 ± 10.69	62.38 ± 9.10	0.136
Left atrial diameter (mm), mean ± SD	45.04 ± 5.88	44.25 ± 8.56	0.799
Prognosis, n (%)			0.003
Good	51 (47.7)	46 (70.8)	
Poor	56 (52.3)	19 (29.2)	

SD = standard deviation; NIHSS = National Institutes of Health Stroke Scale; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; INR = international normalized ratio; Fib = fibrinogen; Hcy = homocysteine; EF = ejection fraction

Comparison of Data from Supplementary Examinations

The supplementary examinations between the stenosis group and the non-stenosis group showed no statistical differences in LDL, TC, TG, INR, Fib, Hcy, EF, or left atrial diameter ($P > 0.05$) (Table 1). Patients in the non-stenosis group had a significantly better prognosis at follow-up than those in the stenosis group ($P = 0.003$).

Analysis of the Types of Cerebral Infarction Lesions

The distribution of infarction lesions is shown in Table 2. Infarction lesions in the two groups were classified into single infarction lesion and multiple infarction lesions. A total of 105/172 patients (61.0%) had a single infarction lesion, with 79/107 patients (73.8%) in the stenosis group and 26/65 patients (40.0%) in the non-stenosis group. A total of 67/172 patients (39.0%) had multiple infarction lesions, with 28/107 patients (26.2%) in the stenosis group and 39/65 patients (60.0%) in the non-stenosis group. Comparison between the two groups showed that the number of lesions was significantly different ($P = 0.026$) (Table 3).

Comparison of the size of the lesion area between the two groups revealed that 43/172 patients (25.0%) had massive infarction lesions, with 25/107 patients (23.3%) in the stenosis group and 18/65 patients (27.7%) in the non-stenosis group, showing no significant difference ($P = 0.505$) (Table 3).

Subgroup Analyses

The total number of cerebral artery stenosis segments was 278. Among them, there were 48 lesion in extracranial arteries (17.3%) and 230 in intracranial arteries (82.7%). The top 3 affected cerebral artery

Table 2. Types of infarction lesions in the two patient groups

Type of lesion	Stenosis group ($n=107$)	Non-stenosis group ($n=65$)
Single lesion, *n* (%)	79 (73.8)	26 (40.0)
Single anterior circulation lesion		
Cortical-subcortical	24 (22.4)	12 (18.5)
Cortical	6 (5.6)	4 (6.2)
Subcortical		
Diameter ≥ 15 mm	13 (12.1)	7 (10.8)
Diameter < 15 mm	17 (15.9)	1 (1.5)
Single posterior circulation lesion*	7 (6.5)	2 (3.1)
Watershed	12 (11.2)	0 (0)
Multiple lesions, *n* (%)	28 (26.2)	39 (6.0)
Unilateral anterior circulation	15 (14.0)	19 (29.2)
Unilateral posterior circulation	4 (3.7)	5 (7.7)
Unilateral anterior circulation + posterior circulation	0 (0)	0 (0)
Bilateral anterior circulation	6 (5.6)	11 (16.9)
Bilateral posterior circulation	2 (1.9)	2 (3.1)
Bilateral anterior circulation + posterior circulation	1 (0.9)	2 (3.1)

*: Single posterior circulation lesion especially refers to brain stem and cerebellar infarction

Table 3. Comparison of the number and size of lesions in the two patient groups

Variables	Stenosis group ($n=107$)	Non-stenosis group ($n=65$)	*P*
Number of lesions, *n* (%)			0.026
Single	79 (73.8)	26 (40.0)	
Multiple	28 (26.2)	39 (60.0)	
Diameter of lesions (mm), *n* (%)			0.505
≥ 40	25 (23.3)	18 (27.7)	
< 40	82 (76.7)	47 (72.3)	

segments were the MCA ($n=114$, 48.1%), ACA ($n=39$, 14.0%), and PCA ($n=35$, 12.6%). There were 53 cases (49.5%) of intracranial artery stenosis, 25 cases (23.4%) of extracranial artery stenosis, and 29 cases (27.1%) of simultaneous intracranial and extracranial artery stenosis (**Supplementary Table 1**). We compared the baseline data among the four groups: intracranial stenosis, extracranial stenosis, intracranial and extracranial stenosis, and non-stenosis. Age ($P<0.001$), CHA_2DS_2-VASc score ($P<0.001$), NIHSS score ($P=0.001$), hypertension ($P<0.001$), history of stroke/TIA ($P<0.001$), coronary artery disease ($P=0.001$), diabetes ($P=0.003$), and prognosis ($P=0.008$) were significantly different among the four groups (**Supplementary Table 2**).

Factors Associated with Risk of 3-Month Poor Prognosis

Supplementary Table 3 shows the characteristics of the patients according to their 3-month prognosis. During follow-up, only antithrombotic treatments and blood pressure were recorded. Seven patients with incomplete data (blood pressure and/or medication) were not included in the analysis, leaving 165 included patients. The results showed that the independent risk factors for poor prognosis of nonvalvular atrial fibrillation with cerebral infarction were higher NIHSS score (OR=1.458, 95%CI: 1.226–1.679, $P<0.001$), without continuous anticoagulant therapy (OR=0.182, 95%CI: 0.062–0.532, $P=0.002$), and history of stroke/TIA (OR=4.377, 95%CI: 1.361–14.083, $P=0.013$) (**Table 4**).

Discussion

The aim of this study was to investigate patients with cerebral infarction and NVAF and compare the characteristics of the two groups of patients, i.e., those

Table 4. Multivariate logistic regression analysis for independent risk factors related to the 3-month prognosis

Variables	OR (95% CI)	*P*
Age	1.048 (0.987-1.112)	0.129
History of stroke or TIA	4.377 (1.361-14.083)	0.013
Coronary artery disease	2.504 (0.539-11.645)	0.242
Hypertension	1.509 (0.432-5.273)	0.519
Diabetes	2.289 (0.456-11.481)	0.827
Peripheral vascular disease	0.976 (0.093-10.073)	0.978
Cerebral arterial stenosis	0.604 (0.180-2.030)	0.413
CHA_2DS_2-VASc score	1.006 (0.534-1.896)	0.985
NIHSS score	1.458 (1.226-1.679)	<0.001
Continuous anticoagulant therapy	0.182 (0.062-0.532)	0.002

NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack; OR = odds ratio; CI = confidence interval

who also had cerebral artery stenosis vs. those without cerebral artery stenosis, with the aim of understanding more about NVAF in combination with cerebral artery stenosis. The results showed that the patients in the stenosis group had a higher mean age and higher rates of history of hypertension and stroke than those in the non-stenosis group. The patients with stenosis also had a worse prognosis at follow-up, but multivariate analysis suggested that stenosis was not a risk factor for worse prognosis. The only factor found to be an independent risk factor was the NIHSS score. These results highlight the existence of cerebral artery stenosis in combination with NVAF.

In recent years, with the development of imaging technology for vascular examination and the gradual improvement of cerebral artery stenosis detection rates, the phenomenon of stroke in atrial fibrillation complicated with cerebral atherosclerosis and its relationship with stroke incidence has received increasing attention. Kim *et al.*[20] applied DSA and MRA examinations combined with the $CHADS_2$ scoring system for stroke patients with NVAF and then found that the proportion of intracranial and extracranial atherosclerosis increased with increasing $CHADS_2$ score; therefore, they believed that hypertension, ≥ 75 years of age, and history of stroke/TIA were determinants of complicated cerebral atherosclerosis in patients with NVAF. Our study found that two-thirds cases of NVAF complicated with cerebral infarction had cerebral arterial stenosis. In addition, compared with the non-stenosis group, significant increases were found in the proportion of patients with advanced age, a history of hypertension, and a history of stroke/TIA, as well as in corresponding CHA_2DS_2-VASc score in the stenosis group. Therefore, hypertension, ≥ 75 years of age, and history of stroke/TIA not only are important components and predictive factors for the risk stratification of stroke in atrial fibrillation but also are closely correlated with cerebral infarction patients with NVAF complicated with cerebral artery stenosis, suggesting that cerebral artery stenosis has a potential effect on the occurrence and development of NVAF complicated with cerebral infarction.

In addition, cerebral artery stenosis may also aggravate the condition of patients with NVAF complicated with cerebral infarction. In this study, the mean NIHSS score in the stenosis group was evidently higher than that in the non-stenosis group, with a statistically significant difference, which might be explained by relatively poor cerebral vascular compensation in cerebral infarction patients with NVAF accompanied by cerebral artery stenosis.

In the CHA_2DS_2-VASc stratification scheme[17], new-onset vascular diseases (previous history of myocardial infarction, peripheral arterial disease, or large artery plaque) were considered as the risk factors of stroke in atrial fibrillation. Moreover, these factors are all caused by long-term atherosclerosis. Meanwhile, risk factors including advanced age, hypertension, and diabetes increase the incidence of cerebral atherosclerosis, finally resulting in increased risk of cerebral infarction. At present, the development and popularization of vascular imaging are rapid; therefore, we suppose that cranial artery stenosis could be included into the risk stratification of stroke in atrial fibrillation and may have a more intuitive effect on the determination of the risk of stroke in atrial fibrillation.

The original intention of establishing a stratification scheme for stroke risk in patients with atrial fibrillation is to reasonably assess the risk of complicated cerebral infarction in patients with atrial fibrillation and to guide the choice of the strategy for the

prevention of thromboembolism. Hypertension, ≥ 75 years of age, history of stroke/TIA, and diabetes are considered as acknowledged risk factors for stroke in atrial fibrillation; however, the mechanisms of these factors serving as its determinants are still unclear. Generally, hypertension and advanced age are supposed to cause changes in cardiac structure, especially corresponding abnormal hemodynamics and slowed left atrial appendage blood flow velocity following left atrial enlargement, promoting thrombogenesis. In addition, hypercoagulability in the presence of diabetes and atrial fibrillation may lead to thrombogenesis. These factors can increase the risk of stroke and underline the complexity of multiple factors or mechanisms in cerebral infarction patients with NVAF. Obviously, the existing research data focused more on the mechanism that the shedding of cardiogenic emboli causes embolic cerebral infarction, which has already been confirmed by heart color Doppler ultrasound and transesophageal echocardiography detecting left atrium and/or left atrial appendage thrombus; however, no evidence of cardiogenic emboli was found in about 70% patients with NVAF[21]. Data even show that only 10% of the cerebral infarctions in patients with atrial fibrillation are caused by left atrial thrombi[21]. Benbir *et al.*[11] pointed out that the pathogenesis of cerebral infarction in patients with NVAF is not only cardiac embolism but also non-cardiac embolism. The Guidelines for the Management of Atrial Fibrillation in the United States pointed out that as many as 25% of the strokes in atrial fibrillation may be caused by cerebrovascular diseases and other cardiogenic emboli or aortic plaques[22]. In patients with NVAF, cerebral artery stenosis also can be complicated; moreover, cerebral artery stenosis is the core link resulting in atherothrombotic cerebral infarction[23].

Our study found that in the cases of NVAF complicated with cerebral infarction, the proportion of cerebral artery stenosis was relatively high (62.2%), suggesting that cerebral artery stenosis may play a role in the occurrence and development of cerebral infarction in patients with NVAF. Kim *et al.*[20] reported that the main pathogenesis of atherothrombotic stroke is artery-to-artery embolism caused by proximal atherosclerotic plaques, so proximal arterial lesions indeed can lead to the occurrence of cerebral infarction in partial patients with NVAF. In addition, high $CHADS_2$ score not only increases the risk of cardiac embolism but also increases the risk of atherosclerotic thrombosis.

Previous studies indicated that cardiac embolism caused by atrial fibrillation is mostly embodied as multiple intracranial infarction or massive infarction caused by arterial occlusion[24]. In the present study, the types of lesions in the non-stenosis group were similar to this characteristic, with 60.0% being multiple cranial infarction and 27.7% being massive infarction, suggesting that cerebral infarction in patients with NVAF without cerebral artery stenosis occurs mainly through the mechanism of cardiac embolism. Nevertheless, the types of lesions in the stenosis group were more varied, including multiple infarction (26.2%), massive infarction (23.3%), watershed infarction (11.2%), and lacunar infarction (15.9%). Compared with the non-stenosis group, the types of lesions and mechanisms in the stenosis group were more complex, so as well as cardiac embolism being an important mechanism other mechanisms are likely to be involved including arterial embolism and hemodynamics based on cerebral artery stenosis[20, 23] (as shown in **Fig. 1**). Our study found 12 cases of watershed infarction (as shown in **Fig. 2**). The potential mechanism of NVAF complicated with cerebral watershed infarction may be based on cerebral artery stenosis, when irregular cardiac contraction occurs with atrial fibrillation this causes abnormal hemodynamics and thereby leads to a deficiency in cerebral blood flow perfusion and consequently cerebral infarction. In addition, 5 cases of subcortical lesion with diameter <15 mm, also known as lacunar cerebral infarction, were detected (as shown in **Fig. 3**). Seifter *et al.*[25] emphasized that cardiac stroke can also cause relatively small subcortical cerebral infarction, but its mechanisms are complex, and these may be cardiac embolism, perforating artery occlusion, or hyaline degeneration of perforating arteries caused by cerebral atherosclerosis of patients with atrial fibrillation themselves resulting in classical lacunar cerebral infarction.

In summary, the pathogenesis of cerebral infarction in patients with NVAF combined with cerebral artery stenosis is complex. The cerebral infarction can be caused by not only cardiac embolism but also non-cardiac embolism such as artery-to-artery embolism, hemodynamic changes, and perforating artery occlusion.

This study is a retrospective study, with a limited period and small sample size; any missing information cannot be obtained, and there might be selection bias in the collection of case data. This study failed to collect cases of NVAF without cerebral infarction as controls, to understand their onset of cerebral artery stenosis. The diagnosis of cerebral artery stenosis in this study mainly relied on MRA, which has a relatively low positive predictive value, resulting in a possible lack of accuracy in the diagnosis of cerebral artery stenosis. This study did not detect serum markers that can reflect the risk of stroke in atrial fibrillation, such

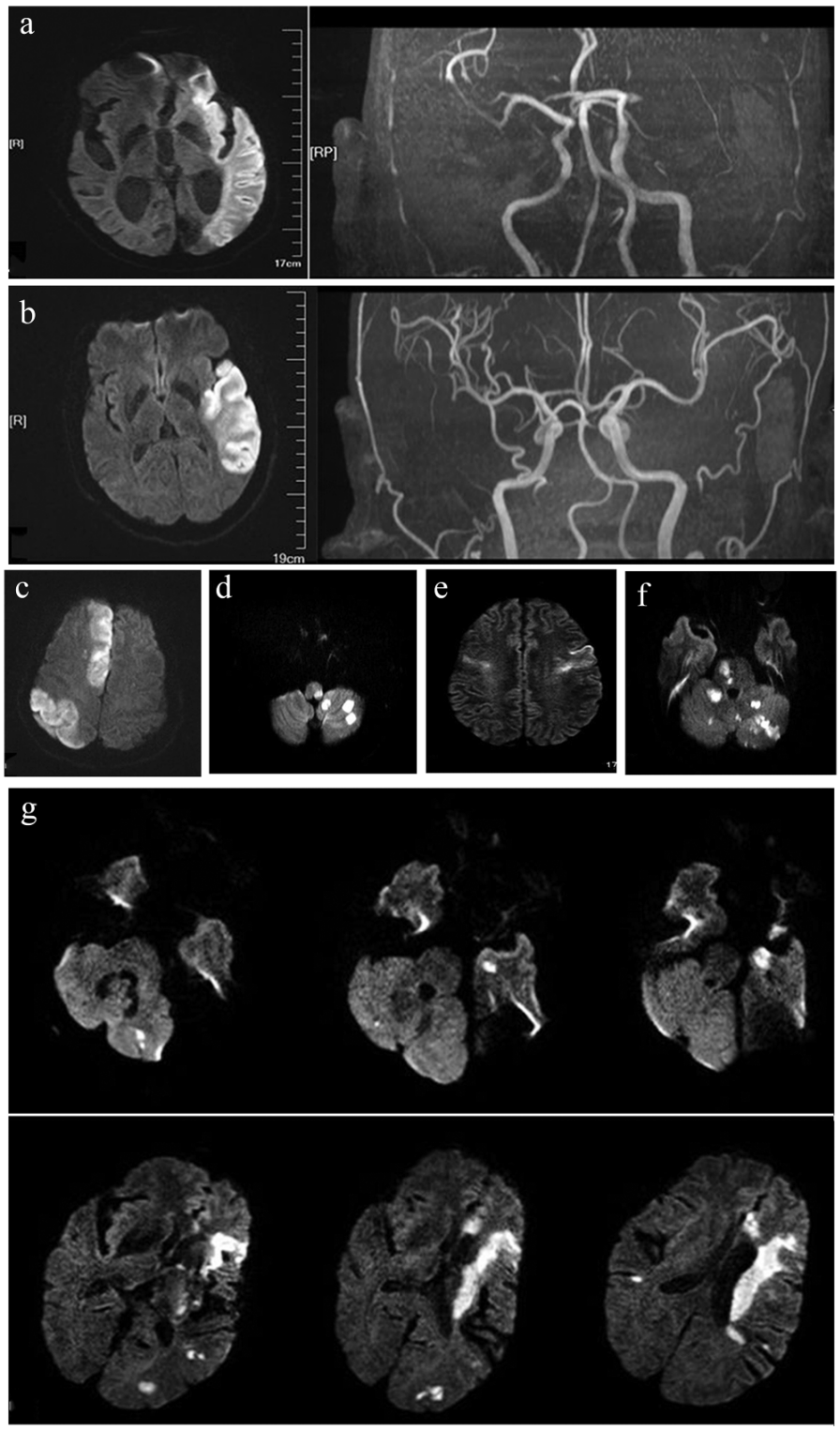

Fig. 1. Typical types of cerebral infarction as shown by cranial MRI

(a): massive infarction in the left frontal, temporal, and parietal lobes, left MCA occlusion, right MCA, and VA stenosis; (b): massive infarction in the left temporal and parietal lobes, no obvious stenosis in MRA; (c): multiple anterior circulation infarction; (d): multiple posterior circulation infarction; (e): bilateral anterior circulation infarction; (f): bilateral posterior circulation infarction; and (g): anterior and posterior circulation infarction.

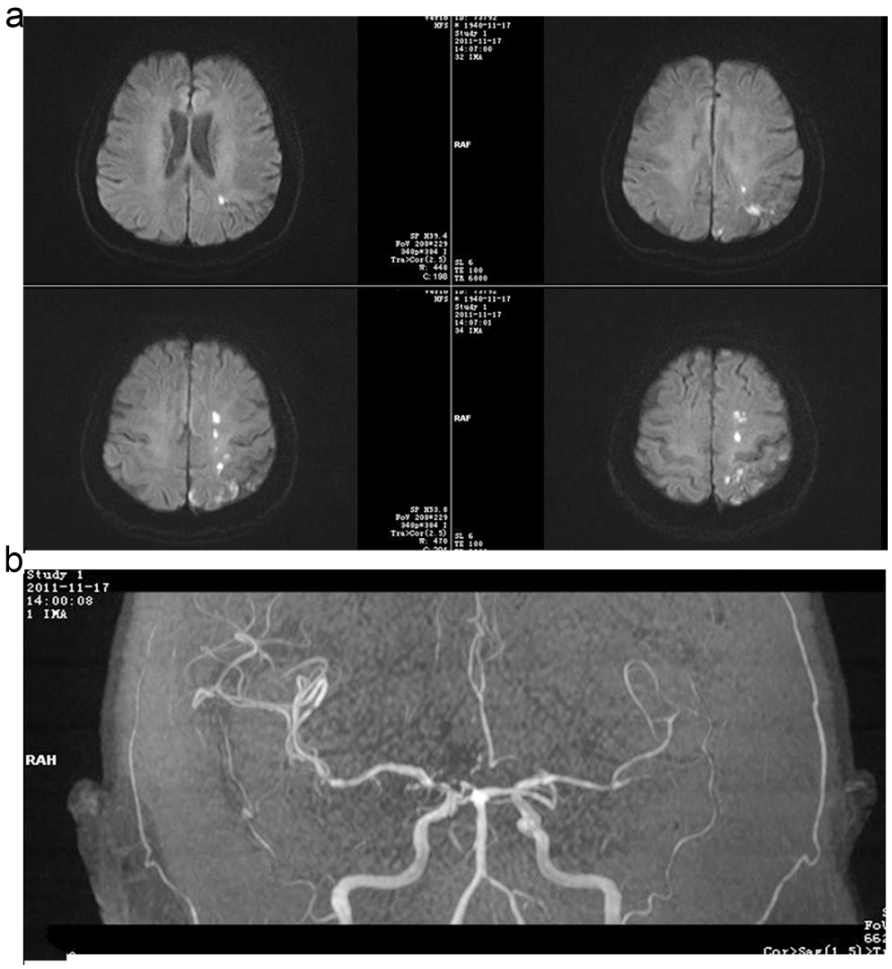

Fig. 2. Watershed infarction and its intracranial artery MRA

(a): cord-like acute infarction in the left frontal and parietal lobes; and (b): branches of left anterior cerebral arteries and middle cerebral arteries are reduced.

as D-dimer, C reactive protein, and brain natriuretic peptide. Due to the costs of the examination, only a small number of patients underwent the evaluation of the aortic arch with transesophageal echocardiography or digital subtraction angiography. In addition, because of the retrospective nature of the study and limited financial resources, we could not recontact de patients and ask them to undergo additional examinations. Therefore, the data were far from being complete, and we cannot provide any reliable numbers or analyses to assess aortic arch plaques. Finally, there were a wide variety of combinations of unilateral/bilateral lesions with unilateral/bilateral stenosis, and the sample size was too small to perform analyses based on this grouping. Multicenter studies will have to address this issue.

Conclusions

Advanced age, hypertension, and history of stroke/TIA rates were higher in patients with cerebral infarction and NVAF combined with cerebral artery stenosis than in patients who had no cerebral artery stenosis. There were many types of cerebral infarction lesions in patients with NVAF combined with cerebral artery stenosis, suggesting that the pathogenesis of cerebral infarction may be both atherosclerotic cerebral infarction and cardiac embolism in these patients.

Conflict of Interests

All authors declare that they have no conflict of interests.

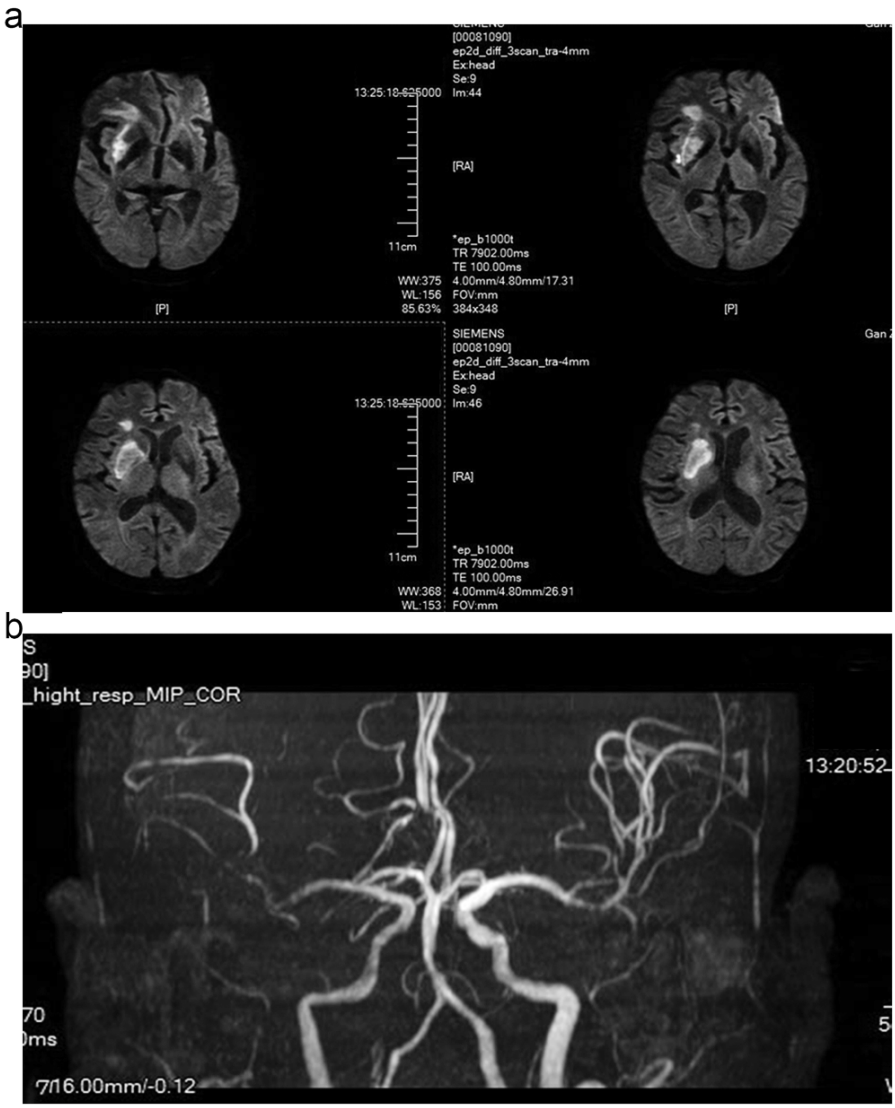

Fig. 3. Subcortical infarction and its intracranial artery MRA

(a): flaky acute infarction in the right basal ganglia region; and (b): branches with obvious stenosis in the M1 and M2 segments of right middle cerebral artery branches are reduced, basilar artery stenosis.

Acknowledgments

Not applicable.

References

1) Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D, American Heart Association Stroke Council, Council on Cardiovascular Nursing Council on Clinical Cardiology, Interdisciplinary Council on Quality of, Care Outcomes, Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. Stroke, 2011; 42: 227-276.
2) Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular, Stroke Nursing, Council on Clinical Cardiology, Council on Peripheral Vascular, Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2014; 45:

2160-2236.
3) Marini C, De Santis F, Sacco S. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke, 2005; 6: 1115-1119.
4) Klein HH TH. Cardioversion in Non-Valvular Atrial Fibrillation. Dtsch Arztebl Int, 2015; 112: 856-862.
5) Stroke Risk in Atrial Fibrillation Working G. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. Stroke, 2008; 39: 1901-1910.
6) Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and Thromboembolism in Atrial Fibrillation. Circulation Journal, 2012; 76: 2289-2304.
7) Jover E MF, Roldán V, Montoro-García S, Valdés M, Lip GY. Atherosclerosis and thromboembolic risk in atrial fibrillation: focus on peripheral vascular disease. Ann Med, 2013; 45: 274-290.
8) Bogousslavsky J, Van Melle G, Regli F. Pathogenesis of anterior circulation stroke in patients with nonvalvular atrial fibrillation: the Lausanne Stroke Registry. Neurology, 1990; 40: 1046-1050.
9) Miller VT, Rothrock JF, Pearce LA. Ischemic stroke in patients with atrial fibrillation: effect of aspirin according to stroke mechanism. Stroke Prevention in Atrial Fibrillation Investigators. Neurology, 1993; 43: 32-36.
10) Chang YJ, Ryu SJ, Lin SK. Carotid artery stenosis in ischemic stroke patients with nonvalvular atrial fibrillation. Cerebrovasc Dis, 2002; 13: 16-20.
11) Benbir G, Uluduz D, Ince B, Bozluolcay M. Atherothrombotic ischemic stroke in patients with atrial fibrillation. Clin Neurol Neurosurg, 2007; 109: 485-490.
12) Proietti M, Calvieri C, Malatino L, Signorelli S, Corazza GR, Perticone F, Vestri AR, Loffredo L, Davi G, Violi F, Basili S. Relationship between carotid intima-media thickness and non valvular atrial fibrillation type. Atherosclerosis, 2015; 238: 350-355.
13) Bekwelem W, Jensen PN, Norby FL, Soliman EZ, Agarwal SK, Lip GY, Pan W, Folsom AR, Longstreth WT Jr, Alonso A, Heckbert SR, Chen LY. Carotid Atherosclerosis and Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities Study. Stroke, 2016; 47: 1643-1646.
14) Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke, 1991; 22: 983-988.
15) Investigators W-ASIDWT. Design, progress and challenges of a double-blind trial of warfarin versus aspirin for symptomatic intracranial arterial stenosis. Neuroepidemiology, 2003; 22: 106-117.
16) collaborators. NASCET. Benefcial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med, 1991; 325: 445-453.
17) Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest, 2010; 137: 263-272.
18) Fisher CM. Lacunar strokes and infarcts: a review. Neurology, 1982; 32: 871-876.
19) Hofmeijer J, Worp HB, Kappelle LJ. Treatment of space-occupying cerebral infarction. Crit Care Med, 2003; 31(2):617-625. Crit Care Med, 2003; 31(2): 617-625.
20) Kim YD, Cha MJ, Kim J, Lee DH, Lee HS, Nam CM, Nam HS, Heo JH. Increases in cerebral atherosclerosis according to CHADS2 scores in patients with stroke with nonvalvular atrial fibrillation. Stroke, 2011; 42: 930-934.
21) Hart RG, Halperin JL. Atrial fibrillation and stroke : concepts and controversies. Stroke, 2001; 32: 803-808.
22) Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Task Force on Practice Guidelines, American College of Cardiology American Heart Association, Committee for Practice Guidelines, European Society of Cardiology, Euopean Heart Rhythm, Association Heart Rhythm, Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J, 2006; 27: 1979-2030.
23) Depta JP, Bhatt DL. Atherothrombosis and atrial fibrillation: Important and often overlapping clinical syndromes. Thromb Haemost, 2010; 104: 657-663.
24) T. Wessels, C. Wessels, A. Ellsiepen, I. Reuter. Contribution of diffusion-weighted imaging in determination of stroke etiology. AJNR Am J Neuroradiol, 2006; 27: 35-39.
25) Seifert T, Enzinger C, Storch MK, Pichler G, Niederkorm K, Fazekas F. Acute small subcortical infarctions on diffusion weighted MRI: clinical presentation and aetiology. J Neurol Neurosurg Psychiatry, 2005; 76: 1520-1524.

Supplementary Table 1. Distribution of cerebral artery stenosis

Segments	Numbers (n = 278)
Extracranial artery, n (%)	48 (17.3)
E-ICA	18 (6.5)
CCA	12 (4.3)
ECA	3 (1.1)
E-VA	15 (5.4)
Intracranial artery, n (%)	230 (82.7)
I-ICA	22 (7.9)
ACA	39 (14.0)
MCA	106 (38.1)
PCA	35 (12.6)
BA	13 (4.7)
VA	15 (5.4)

Supplementary Table 2. Clinical characteristic of the intracranial stenosis, extracranial stenosis, intracranial and extracranial stenosis and non-stenosis subgroups

Variables	Intracranial Stenosis (n = 53)	Extracranial stenosis (n = 25)	Intracranial and extracranial stenosis (n = 29)	Non-stenosis (n = 65)
Gender, n (%)				
Male	32 (60.4)	12 (48.0)	20 (66.0)	31 (47.7)
Female	21 (39.6)	13 (52.0)	9 (31.0)	34 (53.3)
Age (years), mean ± SD	73.1 ± 8.3[a,c]	74.1 ± 9.7[a]	77.6 ± 8.1[a]	63.4 ± 10.0
History of stroke/TIA, n (%)	26 (49.0)[a,c]	10 (40.0)[a,c]	23 (79.3)[a]	9 (13.8)
Coronary artery disease, n (%)	4 (7.5)[b,c]	6 (24.0)	11 (37.9)[a]	6 (9.2)
Hypertension, n (%)	36 (67.9)[a,c]	17 (68.0)[a,c]	27 (93.1)[a]	18 (27.7)
Diabetes, n (%)	4 (7.5)[c]	2 (8.0)[c]	10 (34.5)[a]	7 (10.7)
Heart failure, n (%)	4 (7.5)	2 (8.0)	5 (17.2)	8 (12.3)
Peripheral vascular disease, n (%)	3 (5.7)	4 (16.0)	4 (7.5)	6 (20.7)
CHA_2DS_2-VASc score, mean ± SD	3.0 ± 1.9[a,c]	3.3 ± 2.0[a,c]	5.1 ± 1.8[a]	1.0 ± 1.0
Smoking, n (%)	26 (49.1)	8 (32.0)	13 (44.8)	21 (32.3)
Alcohol consumption, n (%)	22 (41.5)	10 (40.0)	10 (34.5)	17 (26.2)
NIHSS score, mean ± SD	8.68 ± 6.12[a,c]	7.45 ± 6.24	9.89 ± 6.04[a]	4.59 ± 3.51
History of antiplatelet drugs, n (%)	19 (35.8)	8 (32.0)	11 (37.9)	15 (23.1)
History of anticoagulant drugs, n (%)	3 (5.7)	2 (8.0)	3 (10.3)	6 (9.2)
LDL-C (mmol/L), mean ± SD	2.77 ± 0.61	2.52 ± 0.55	2.86 ± 0.43	2.66 ± 0.66
TC (mmol/L), mean ± SD	3.98 ± 0.91	3.53 ± 0.60	3.90 ± 0.80	4.04 ± 1.25
TG (mmol/L), mean ± SD	1.32 ± 0.91	1.54 ± 0.69	1.89 ± 0.85	1.59 ± 0.94
INR, mean ± SD	1.11 ± 0.20	1.15 ± 0.22	1.21 ± 0.23	1.17 ± 0.41
Fib (g/L), mean ± SD	2.89 ± 0.84	3.56 ± 0.76	3.17 ± 0.78	2.91 ± 0.92
Hcy (μmol/L), mean ± SD	13.08 ± 8.55	13.14 ± 7.98	14.87 ± 8.65	15.37 ± 12.17
EF (%), mean ± SD	65.88 ± 10.08	66.89 ± 10.97	67.41 ± 9.78	62.38 ± 9.10
Left atrial diameter (mm), mean ± SD	44.78 ± 5.97	44.04 ± 4.98	45.43 ± 5.69	44.25 ± 8.56
Prognosis, n (%)				
Good	28 (52.8)[a]	12 (48.0)[a]	11 (37.9)[a]	46 (70.8)
Poor	25 (47.2)	13 (52.0)	18 (62.1)	19 (29.2)

[a] $P < 0.05$, vs. non-stenosis group.
[b] $P < 0.05$, vs. extracranial stenosis group.
[c] $P < 0.05$, vs. intracranial and extracranial stenosis group.

Supplementary Table 3. Clinical characteristic of the patients according to the 3-month good vs. poor prognosis groups

Variables	Good prognosis ($n=95$)	Poor prognosis ($n=70$)	P
Gender, *n* (%)			0.448
Male	50 (52.6)	41 (58.6)	
Female	45 (47.4)	29 (41.4)	
Age (years), mean ± SD	66.01 ± 10.20	75.62 ± 9.00	< 0.001
History of stroke/TIA, *n* (%)	21 (22.1)	42 (60.0)	< 0.001
Cerebral artery stenosis	50 (52.6)	52 (74.3)	0.005
Intracranial stenosis	27 (28.4)	24 (34.3)	
Extracranial stenosis	12 (12.6)	13 (18.6)	
Intracranial and extracranial stenosis	11 (11.6)	15 (21.4)	
Coronary artery disease, *n* (%)	6 (6.3)	19 (27.1)	< 0.001
Hypertension, *n* (%)	37 (38.9)	56 (80.0)	< 0.001
Diabetes, *n* (%)	4 (4.2)	16 (22.9)	< 0.001
Heart failure, *n* (%)	7 (7.4)	10 (14.3)	0.149
Peripheral vascular disease, *n* (%)	3 (3.2)	13 (18.6)	0.001
CHA_2DS_2-VASc score, mean ± SD	1.88 ± 1.60	4.17 ± 2.00	< 0.001
Smoking, *n* (%)	38 (40.0)	27 (38.6)	0.853
Alcohol consumption, *n* (%)	33 (34.7)	23 (32.9)	0.801
NIHSS score, mean ± SD	5.72 ± 4.34	14.83 ± 6.36	< 0.001
History of antiplatelet drugs, *n* (%)	27 (28.4)	24 (34.3)	0.420
History of anticoagulant drugs, *n* (%)	8 (8.4)	6 (8.6)	0.973
LDL-C (mmol/L), mean ± SD	2.76 ± 0.55	2.81 ± 0.53	0.531
TC (mmol/L), mean ± SD	3.92 ± 0.82	4.06 ± 0.84	0.121
TG (mmol/L), mean ± SD	1.54 ± 0.82	1.86 ± 0.88	0.974
INR, mean ± SD	1.13 ± 0.30	1.14 ± 0.21	0.754
Fib (g/L), mean ± SD	2.79 ± 0.76	2.97 ± 0.67	0.492
Hcy (μmol/L), mean ± SD	14.78 ± 8.67	15.96 ± 8.98	0.072
EF (%), mean ± SD	65.56 ± 10.35	62.21 ± 11.28	0.064
Left atrial diameter (mm), mean ± SD	44.56 ± 6.17	44.96 ± 5.97	0.052
Continuous antiplatelet therapy, *n* (%)	36 (37.9)	36 (51.4)	0.083
Continuous anticoagulant therapy, *n* (%)	55 (57.9)	22 (31.4)	0.001
Blood systolic pressure (mmHg), mean ± SD	136.18 ± 11.33	136.57 ± 12.40	0.833
Blood diastolic pressure (mmHg), mean ± SD	83.79 ± 8.01	84.04 ± 7.57	0.837

SD = standard deviation; NIHSS = National Institutes of Health Stroke Scale; LDL-C = low density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; INR = international normalized ratio; Fib = fibrinogen; Hcy = homocysteine; EF = ejection fraction.